

## Comparison of Hemochron and HemoTec Activated Coagulation Time Target Values During Percutaneous Transluminal Coronary Angioplasty

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**Objectives.** The aim of this study was to determine whether activated coagulation time measurements from Hemochron and HemoTec machines can be used interchangeably and whether similar activated coagulation time target ranges for adequate anticoagulation can be applied to both machines.

**Background.** Adequate anticoagulation is necessary for the safe performance of intravascular interventions such as percutaneous transluminal coronary angioplasty. In current practice, anticoagulation status is frequently assessed by way of the activated coagulation time with one of two commercially available systems, HemoTec and Hemochron. Each one employs a different technique to determine the time of clot formation; however, the same target activated coagulation time values for adequate anticoagulation have been used interchangeably in published studies.

**Methods.** A total of 311 paired samples were compared in 113 high risk patients undergoing angioplasty enrolled in a randomized trial of a platelet glycoprotein IIb/IIIa receptor antibody. Simultaneous activated coagulation time measurements were obtained before and after administration of heparin, and the difference between the values of both machines was calculated. The

relation between the Hemochron and HemoTec values was determined by using linear regression analysis. All activated coagulation time measurements were classified as either therapeutic or subtherapeutic using an arbitrary activated coagulation time target of 300 s.

**Results.** There was a correlation between values from the two machines ( $r = 0.86$ ), but the Hemochron values were consistently higher than the HemoTec values by a mean value  $\pm$  SD of  $28 \pm 29\%$ , with wide individual variation. After heparin administration, there was a significant ( $p < 0.0001$ ) difference between the number of measurements classified as therapeutic by HemoTec (53%) and by Hemochron (94%).

**Conclusions.** HemoTec and Hemochron activated coagulation time measurements cannot be used interchangeably. Appropriate target activated coagulation time ranges to determine adequate anticoagulation during coronary angioplasty need to be established for both machines; the target range for one machine should not be extrapolated to the other.

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The need for adequate anticoagulation during percutaneous transluminal coronary angioplasty has been recognized from the very onset of the clinical application of this intervention (1). The current practice in many catheterization laboratories is to assess the degree of anticoagulation by means of the activated coagulation time. A target value of 300 s has been widely touted as indicating adequate anticoagulation, especially in patients with unstable angina or in those undergoing treatment of complex lesions (2,3).

The activated coagulation time initially described by Hattersley (4) in 1966 measures the time it takes for whole blood samples to clot after contact activation. Because this test reflects the activity of heparin administered during any cardiovascular procedure it has come into widespread clin-

ical use for both cardiopulmonary bypass and interventional cardiology procedures. With broader clinical application, automated techniques have evolved to overcome the limitations of the manual techniques originally described by Hattersley and used in the early days of cardiopulmonary bypass.

There are at present two commercially available systems for automated measurements: Hemochron (International Technidyne) and HemoTec (Medtronic HemoTec). Each of these machines uses a different mechanical technique to determine the time of clot formation. The HemoTec machine uses a mechanical plunger that is dipped in and out of kaolin-activated blood samples in cartridges. The machine optically senses the time that it takes the plunger to move through the blood specimen in the cartridge; clotting time is defined as the time at which a certain "drop time" threshold for the plunger is reached. Two types of cartridges are available for use with whole blood: low and high range; these use different kaolin activators and have different sensitivities to heparin. The Hemochron machine uses a magnet inside prewarmed glass specimen tubes that may hold several different activators (usually

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diatomaceous earth for cardiovascular applications). After blood is placed in the tubes, the tubes are rotated inside the machine. As the blood clots, it displaces the magnet, thereby activating a proximity switch. The clotting time is the time it takes to displace the magnet a given distance. There are no published direct comparisons of the two systems. Target activated coagulation time values for adequate anticoagulation have been used interchangeably in published reports (5). The purpose of this study is to determine whether there is a relation between HemoTec and Hemochron activated coagulation times and to determine if they can be used interchangeably to assess anticoagulation during coronary angioplasty.

### Methods

A total of 311 paired simultaneous HemoTec and Hemochron activated coagulation time measurements were obtained in 113 patients enrolled in a randomized trial of a platelet glycoprotein IIb/IIIa receptor antibody (7E3, Centocor) for high risk coronary angioplasty. All patients gave written informed consent, and the study was approved by the institutional research review committee. High risk coronary angioplasty was defined as including either unstable angina, acute myocardial infarction or high risk lesion morphology (according to American Heart Association/American College of Cardiology A/B/C lesion classification with either two "B" characteristics or one "C" characteristic). Activated coagulation times were measured at baseline, before the administration of heparin ( $n = 83$ ) and one or more times after administration of 10,000 to 15,000 U of heparin during the angioplasty procedure ( $n = 228$ ). All blood samples were obtained from the arterial sheath or the coronary guiding catheter. The difference between each paired measurement was calculated and a percent difference was obtained by the formula: % difference = (Hemochron ACT - HemoTec ACT)/(HemoTec ACT); where ACT = activated clotting time.

Percent differences were calculated for grouped baseline activated coagulation times, postheparin activated coagulation times and all activated coagulation times. The relation between HemoTec and Hemochron activated coagulation times was then determined by using linear regression.

To assess the comparability of target activated coagulation times, all postheparin activated coagulation time measurements were classified as either therapeutic or subtherapeutic, using an arbitrarily chosen activated coagulation time target of 300 s for both Hemochron and HemoTec measurements. Results of the two measurement systems were compared by using chi-square analysis. A  $p$  value  $<0.05$  was considered statistically significant for all analyses.

### Results

A total of 311 simultaneous paired measurements were obtained. All values are presented as mean  $\pm$  SD. There was

**Table 1. HemoTec and Hemochron Activated Clotting Times Before and After Heparin**

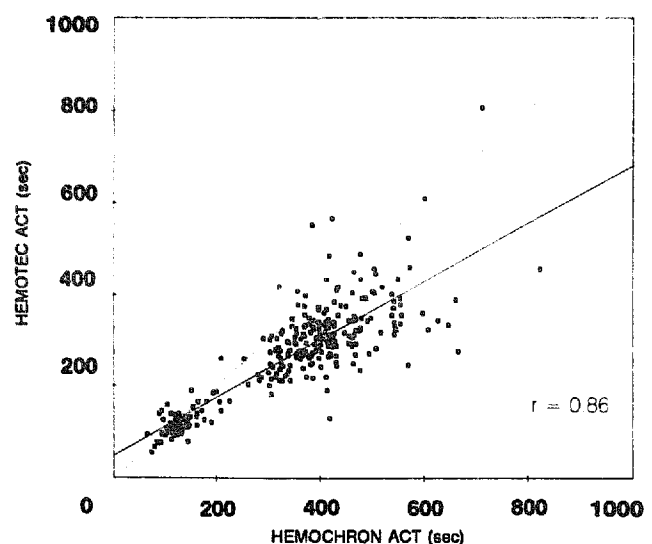
	Mean HemoTec ACT (s)	Mean Hemochron ACT (s)	Mean Difference	
			s	%
Before heparin ( $n = 83$ )	114 $\pm$ 23	125 $\pm$ 25	11 $\pm$ 23	12 $\pm$ 20
After heparin ( $n = 228$ )	314 $\pm$ 86	414 $\pm$ 114	99 $\pm$ 86	34 $\pm$ 29
Total ( $n = 311$ )	262 $\pm$ 116	338 $\pm$ 161	76 $\pm$ 84	28 $\pm$ 29

All values are expressed as mean value  $\pm$  SD. ACT = activated clotting time.

a mean difference of  $76 \pm 84$  s between all HemoTec and Hemochron measurements (mean percent difference  $28 \pm 29\%$ ). When measurements were grouped into baseline ( $n = 83$ ) and postheparin measurements ( $n = 228$ ), there was a mean difference in baseline activated coagulation time of  $11 \pm 23$  s (mean percent difference  $12 \pm 20\%$ ) and a mean difference in postheparin activated coagulation time of  $99 \pm 86$  s (mean percent difference  $34 \pm 29\%$ ) (Table 1).

There was a significant linear relation between HemoTec and Hemochron activated coagulation times (Fig. 1). Despite a relatively strong correlation coefficient ( $r = 0.86$ ), there was considerable individual variation. The fitted line clearly diverged from the line of identity according to the equation: HemoTec ACT =  $48.67 + 0.63 \times$  (Hemochron ACT), where ACT = activated clotting time. There was an obvious increase in variability of the relation between the two activated coagulation time measurements after the administration of heparin.

**Figure 1. Relation between simultaneous Hemochron (x axis) and HemoTec (y axis) activated coagulation times. The dotted line represents the line of identity. The solid line represents the fitted equation: HemoTec ACT =  $48.67 + 0.63 \times$  (Hemochron ACT), where ACT = activated clotting time.**



**Table 2.** Application of a 300-Second Target to 228 Paired Postheparin HemoTec and Hemochron Activated Clotting Times

	Hemochron <300 s	Hemochron ≥300 s
HemoTec <300 s	11	94
HemoTec ≥300 s	1	122

$p < 0.0001$  by chi-square analysis. Values indicate number of measurements.

After the application of an arbitrarily chosen target therapeutic activated coagulation time of 300 s after heparin administration, there were profound differences between the two systems. Of the 228 paired values obtained after heparin administration, 216 (94%) were classified as therapeutic by the Hemochron machine. In contrast, only 123 (53%) were classified as therapeutic by the HemoTec machine. Among a total of 228 postheparin measurements, there were 94 (41%) in which the Hemochron activated coagulation time was therapeutic but the HemoTec activated coagulation time was subtherapeutic, and only 1 measurement (0.4%) with a therapeutic HemoTec activated coagulation time but a subtherapeutic Hemochron activated coagulation time (Table 2).

## Discussion

**Background.** Intravenous heparin is routinely administered during coronary angioplasty to prevent the formation of thrombus at the site of balloon injury to the vessel wall. However, no true standards exist as to what constitutes adequate heparinization for coronary angioplasty (2,3).

Currently, the method most commonly used to assess the degree of anticoagulation during an angioplasty procedure is the activated coagulation time. This method, initially described as a manual technique by Hattersley (4), is now available for rapid bedside monitoring with automated methods, and it has a linear correlation with the dose of intravenously administered heparin (6).

The concept of a target activated coagulation time after heparin administration that indicates adequate anticoagulation and is associated with prevention of thrombus formation dates back to observations made in the early experience with heparin use during extracorporeal circulation for cardiac surgery. Bull et al. (6) noted the absence of visible thrombus in the bypass circuit when the activated coagulation time level was  $\geq 300$  s as assessed by the original method of Hattersley. They (7) also demonstrated that there was a high variability in the activated coagulation time response after a fixed dose of heparin and advocated the routine use of activated coagulation time measurements to guide heparin dosing.

The idea of guided heparin dosing has more recently been extrapolated to other cardiovascular interventional procedures including coronary angioplasty, using 300 s as a minimal safety target (2,3).

**Previous coronary angioplasty studies.** Rath and Bennett (8) reported an intraobserver variability of  $<8\%$  and an interobserver variability of  $<10\%$  with a Hemochron machine. They also compared two protocols for heparin administration. When a bolus of 10,000 U of heparin was administered, 23% and 55% of the patients had an inadequate activated coagulation time (defined by them as  $<250$  s) in the 1st 45 and 60 min of the procedure, respectively. When infusion at a rate of 2,000 U/h was added to the initial bolus, only 5% and 15%, respectively, had an inadequate activated coagulation time at 45 and 60 min.

In another study using the Hemochron machine, Ogilby et al. (9) found that after an intravenous dose of 10,000 U of heparin, 11% of 108 patients had an activated coagulation time of  $<300$  s. In contrast, Dougherty et al. (10) reported that after the same dose of heparin only 13% of their 545 patients had an activated coagulation time  $>300$  s with the HemoTec machine.

Such wide disparities in activated coagulation time heparin response between HemoTec and Hemochron activated coagulation time measurement systems support the findings of the present study. In our study, Hemochron activated coagulation times were consistently higher than HemoTec activated coagulation times despite a good correlation between activated coagulation time measurements on the two devices. When adequate coagulation was arbitrarily defined as an activated coagulation time  $\geq 300$  s, 53% of patients would have been considered to have adequate anticoagulation with the HemoTec device versus 94% with the Hemochron device. These differences between the two automated methods for activated coagulation time measurement must be taken into account when trying to establish an appropriate target activated coagulation time.

**Activated coagulation times and clinical outcome.** There are no prospective studies to date showing that achieving a higher level of anticoagulation is associated with a reduced incidence of complications. Frierson et al. (11) have challenged the concept of a safety range with a retrospective analysis of 201 elective procedures. The mean HemoTec activated coagulation time before balloon inflation was  $<300$  s in 63% of cases after a mean heparin dose of 10,100 U. The overall incidence of acute occlusion was 4%. These investigators found no differences between activated coagulation time before balloon inflation in patients with and without complications although the number of patients with complications was low (only six abrupt closures) and their definition of complication was not entirely clear. McGarry et al. (12) retrospectively reviewed clinical data in 336 patients who underwent coronary angioplasty and found that abrupt closure and ischemic events were significantly reduced in patients with aPTT measurements (6 h after the procedure)  $\geq 3$  times the control value. A recent study by Ferguson et al. (13) showed no differences in baseline HemoTec activated coagulation times between patients with and without major complications after angioplasty (death or emergency or urgent coronary artery bypass grafting). Patients with major

complications had significantly lower postheparin and final activated coagulation times, although they also had a higher level of risk before angioplasty. Patients with postheparin activated coagulation times of <250 s had significantly more complications.

The present study was not designed to assess the relation of activated coagulation time levels to clinical outcome. Future prospective studies are needed to determine whether more aggressive procedural anticoagulation can influence subsequent clinical outcome after angioplasty or whether there is a reasonable target threshold activated coagulation time. However, our findings do emphasize the inappropriateness of comparing HemoTec to Hemochron target activated coagulation times.

**Limitations.** Several limitations to the present study must be considered. The patients enrolled were participants in a randomized, blinded, controlled trial of 7E3, a glycoprotein IIb/IIIa receptor antibody. It is possible, but unlikely, that the presence or absence of the experimental drug could somehow bias the results. There is also some concern about interobserver variability in activated coagulation time measurements, particularly with the Hemochron device, which uses manual mixing of blood and activator. This potential error was reduced by using a limited number of trained personnel with set procedural protocols. It is also possible, but unlikely, that the high risk angioplasty patients involved in this study have unique features that also might bias the study. Unstable angina and acute coronary syndromes may manifest a prothrombotic state, but that should not affect the major findings of this study related to activated coagulation time measurements. Finally, the study group was relatively small, but the sample size was more than adequate to support the findings of the study.

**Conclusions.** We conclude that HemoTec and Hemochron activated coagulation time measurements cannot be used interchangeably. Target activated coagulation time ranges for one machine cannot be extrapolated to the other. Further prospective studies are necessary to determine appropriate levels of anticoagulation for coronary angioplasty, as assessed by both Hemochron and HemoTec activated coagulation times.

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## References

1. Gruntzig AR, Senning a, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis. Percutaneous transluminal coronary angioplasty. *N Engl J Med* 1979;301:61-8.
2. Kulick DL, Kawanishi DT. Percutaneous transluminal coronary angioplasty. In: Kulick DL, Rahimtoola SH, editors. *Techniques and Applications in Interventional Cardiology*. St. Louis (MO): Mosby-Year Book, 1991:43-118.
3. Ellis SG. Elective coronary angioplasty. Technique and complications. In: Topol EJ, editor. *Textbook of Interventional Cardiology*. Philadelphia: Saunders, 1990:199-222.
4. Hattersley PG. Activated coagulation time of whole blood. *JAMA* 1966;196:150-4.
5. Ferguson JJ. All ACTs are not created equal. *Texas Heart Inst J* 1992;19:1-3.
6. Bull BS, Huse WM, Brauer FS, Korpman RA. Heparin therapy during extracorporeal circulation. II. The use of a dose-response curve to individualize heparin and protamine dosage. *J Thorac Cardiovasc Surg* 1975;69:685-9.
7. Bull BS, Korpman RA, Huse WM, Briggs BD. Heparin therapy during extracorporeal circulation. I. Problems in existing heparin protocols. *J Thorac Cardiovasc Surg* 1975;69:674-84.
8. Rath B, Bennett DH. Monitoring the effect of heparin by measurement of activated clotting time during and after percutaneous transluminal coronary angioplasty. *Br Heart J* 1990;63:18-21.
9. Ogilby JD, Kopleman HA, Klein LW, Agarwal JB. Adequate heparinization during PTCA: assessment using activated clotting times. *Cathet Cardiovasc Diagn* 1989;18:206-9.
10. Dougherty KG, Gaos CM, Bush HS, Leachman DR, Ferguson JJ. Activated clotting times and activated partial thromboplastin times in patients undergoing coronary angioplasty who receive bolus doses of heparin. *Cathet Cardiovasc Diagn* 1992;26:260-3.
11. Frierson JH, Dimas AP, Simpfendorfer CC, Pearce G, Miller M, Franco I. Is aggressive heparinization necessary for elective PTCA? *Cathet Cardiovasc Diagn* 1993;28:279-82.
12. McGarry TF, Gottlieb RS, Morganroth J, et al. The relationship of anticoagulation level and complications after percutaneous transluminal coronary angioplasty. *Am Heart J* 1992;123:1445-51.
13. Ferguson JJ, Dougherty KG, Gaos CM, Bush HS, Marsh KC, Leachman DR. The relationship between procedural activated clotting time and post-PTCA outcome. *J Am Coll Cardiol*. In press.